Maclaire (1925); Shinosaki (1926), one case; Vernon (1936); Poulsen (1938); Smith (1939)—first case.

Summary

A case is described of chronic pyelonephritis in which urinary potassium loss resulting in periodic hypokalaemic paralysis dominated the clinical picture. It was estimated by balance data that there was a deficiency of about 1,500 mEq of potassium, amounting to 40% of the total normal body potassium. The differential diagnosis betwen hypokalaemic paralysis of the familial type and that secondary to a renal defect is discussed. No explanation is given for the differential effects of chronic pyelonephritis on renal tubular function.

Thanks are expressed to Dr. R. J. Porter, who first diagnosed the case and arranged transfer to Hammersmith Hospital for balance studies; and to Dr. A. G. Macgregor for the out-patient data. We are indebted to Dr. R. I. S. Bayliss for determination of plasma 17-hydroxycorticosteroids and to Dr. C. L. Cope for determination of compounds E and F in the urine. Mrs. Walwyn-Jones and her staff gave invaluable assistance in supervising the various fixed diets in the balance studies.

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The Library of Congress has just published *Scientific and Technical Serial Publications, United States, 1950–1953.* This bibliography, which covers medical journals and reports, is divided into two sections, dealing respectively with non-government and government publications. Entries are grouped under a subject classification, and an alphabetic index of subject headings is included. Information is given regarding recent changes of titles, publisher, date of first issue, and frequency. The nature of the material included in each journal is indicated (for example, original research, review literature, abstracts, etc.). This work, which should be a useful addition to scientific bibliography, was prepared under the sponsorship of the National Scientific Foundation and can be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., price $1.25.

SIMILARITY OF SYMPTOMATOLOGY OF PREMENSTRUAL SYNDROME AND TOXAEMIA OF PREGNANCY AND THEIR RESPONSE TO PROGESTERONE*

BY

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An investigation was undertaken to ascertain the incidence of premenstrual syndrome in those who had previously suffered from toxaemia of pregnancy. This followed on the finding by Greene and Dalton (1953) of the high incidence of toxaemia of pregnancy (19%) among sufferers of premenstrual syndrome. The study of both diseases revealed a striking similarity of symptoms and signs suggesting a common aetiology. The successful treatment of premenstrual syndrome with progesterone (Gray, 1941; Puech, 1942; Albeaux-Fernet and Loublie, 1946; Greene and Dalton, 1953; and Rees, 1953a) suggested a possible treatment for toxaemia of pregnancy.

The investigation was carried out on 952 women, of whom 237 had suffered from toxaemia of pregnancy. Of these toxaemic mothers 40 were in the partnership practice and the remainder had been under the care of the local authority clinics, whose records were examined for the years 1942–53. Controls were women at a local engineering factory (614), and mothers with children under 5 years attending a routine infant welfare clinic (101). All were interviewed personally by me and set questions were asked. Those not already under treatment for premenstrual syndrome were given a special calendar on which to record the dates of menstruation and any recurrent symptoms during the six weeks immediately following the interview.

Premenstrual syndrome is often difficult to diagnose, for its recognition depends both on the intelligence of the patient and the severity of symptoms, so diagnosis was limited to those whose symptoms fulfilled the following conditions: (1) present in each of the three previous cycles, (2) severity sufficient to demand relief with analgesics or the seeking of medical advice, (3) occurrence at a specific phase of the menstrual cycle, confirmed by calendar and limited to the three premenstrual days, the period of menstruation, or midcycle. The diagnosis of toxaemia was limited to those who gave evidence of a blood pressure of 120/70 mm. Hg or below early in pregnancy, which rose after the 28th week to 140/90 mm. Hg or above, and for which treatment was instituted. Thirty-one cases of toxaemia of pregnancy were excluded owing to uncertain diagnosis or complicating factors—for example, pyelitis, placenta praevia; 96 women with no menstrual loss in the three previous months were excluded.

Results of Investigation

The results (Figs. 1 and 2) show the very high incidence of premenstrual syndrome in toxaemic mothers (86.4%), compared with controls (26.6%), and also show that the incidence of premenstrual syndrome increases in toxaemic mothers from 76.6% after one pregnancy to 100% after four pregnancies. Age had no apparent significance on the incidence.

The time of onset of premenstrual syndrome in toxaemic mothers was stated to be: puberty, 23%; following child-

*The Charles Oliver Hawthorne Prize essay, 1954.

birth, 34.9%; marriage, 2.3%; menopause, 2.9%; and unknown, 36%. While these times of onset may not necessarily be accurate, the fact that 26.2% of toxaemic mothers

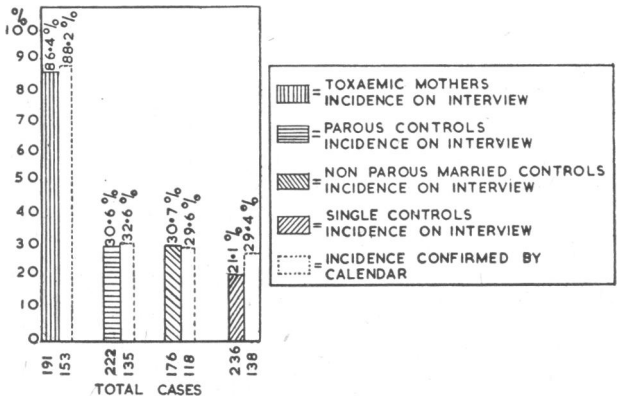

FIG. 1.—Incidence of premenstrual syndrome in toxaemic mothers and controls.

had premenstrual syndrome prior to the toxaemic pregnancy suggests that premenstrual syndrome cannot be regarded as the direct result of toxaemia; nevertheless the effect of a toxaemic pregnancy on an already established case of premenstrual syndrome is usually to increase the severity of the premenstrual symptoms. Graphs of the duration of an attack of premenstrual symptoms and also of its time relation to menstruation were found to show no significant difference between the type of attack experienced by the toxaemic mothers and the controls. The menstrual history of sufferers of premenstrual syndrome, whether toxaemic mothers or controls, was normal in regard to the time of first period, duration of loss, length of cycle, and absence of dysmenorrhoea, which confirms the finding of a normal menstrual history among sufferers of premenstrual syndrome reported by Rees (1953b) and Greene and Dalton (1953).

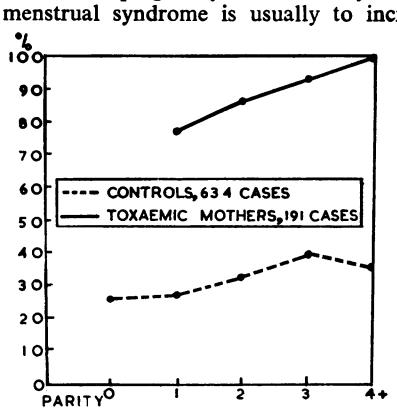

FIG. 2.—Effect of parity on incidence of premenstrual syndrome.

Minor Symptoms in Toxaemia of Pregnancy

Toxaemia of pregnancy is generally regarded as a disease without subjective symptoms, except prior to an eclamptic fit, therefore it was surprising at interview to find the toxaemic mothers describe minor symptoms, which had existed for many weeks or months before the development of signs of toxaemia. This was further confirmed by 92 mothers who had experienced both normal and toxaemic pregnancies; of these mothers 72 (78.3%) noticed the contrast between the sense of wellbeing and absence of symptoms in a normal pregnancy and the malaise and minor symptoms of the toxaemic pregnancy. These minor symptoms, which increase very gradually in severity and which may occur from early pregnancy onwards, include lassitude, hypersomnia, depression, nausea, irritability, headache, vertigo, visual aura, and ulcerative stomatitis, and are all symptoms of premenstrual syndrome. A marked similarity of symptoms in any one individual occurred during the toxaemic pregnancy and the premenstruum, and this was true whether the premenstrual syndrome had its onset before or after the toxaemic pregnancy. Thus, one woman, who recalled the left hemicranial headaches with "black snakes before her eyes" and ulcerative stomatitis during her toxaemic pregnancy, had since suffered from these same symptoms in the premenstruum. The following extract of a patient's letter also illustrates this similarity of symptoms:-

Case 1.—A housewife aged 35 years, whose two pregnancies had been complicated by toxaemia, wrote: "My present trouble started with my first child, but still more so with the second. Roughly 15 days after the period I experience immediate and sudden pain, which forces me to retire unable to retain the straightened posture. This is preceded by a certain amount of white discharge. There is a feeling of being blown out with wind and frequency of passing water. The following day pain has gone but sensation of severe inflammation over entire part from waist down. There is backache, nausea, and complete exhaustion, and I feel really ill, rather as I did when in toxic conditions. Monthly periods completely free from all pain, but are rather slight." This patient became symptom-free on progesterone, 25 mg. alternate days, throughout the cycle and received a 500-mg. progesterone implant in June, 1953, which relieved the symptoms for eleven months.

The symptoms noted in toxaemic mothers during pregnancy and in the premenstruum are compared with the symptoms experienced by controls during the premenstruum in the accompanying Table.

Symptoms in Toxaemic Mothers in Pregnancy and Premenstruum and in Controls During Premenstruum

	Toxaemic Mothers		Controls
	Pregnancy*	Premenstruum	Premenstruum
	%	%	%
Headache	48·2	83·9	90·8
Vertigo	29·2	35·8	27·7
Nausea and vomiting	16·1	26·3	13·3
Visual aura	37·9	12·4	6·3
Lassitude	43·8	9·5	2·9
Depression	9·5	6·6	16·2
Irritability	13·8	10·9	9·2
Backache	5·8	13·8	6·3
Petit mal	1·5	0·7	0·6
Grand mal	5·8	2·2	†

* Excluding symptoms which ceased after the third month of pregnancy.
† Epileptics not eligible for employment at the factory from which most controls were interviewed.

It has been observed during pregnancy that when symptoms similar to those usually experienced in the premenstruum occur with increasing severity, pregnancy may culminate in abortion. It may be that some cases of abortion are due to early toxaemia of pregnancy and are thus analogous to the premature labour so frequent in toxaemia of pregnancy. The following case illustrates this:

Case 2.—A factory worker, aged 28, had progesterone treatment in February, 1952, for premenstrual syndrome, with symptoms of acne of face, nausea, lassitude, and depression, increasing during the premenstrual week and culminating in a headache over the right eye on the first day of menstruation. In May, 1952, she became pregnant and suffered increasing nausea, followed two weeks later by vomiting. At nine weeks she had a severe headache, which lasted seven days instead of the usual one day as in the premenstruum. The increasing severity of headache, vomiting, and photophobia forced her to rest in bed. Seven days after the onset of the headache she had a spontaneous abortion and all symptoms ceased.

Oedema, Hypertension, and Albuminuria in Premenstrual Syndrome

Day-to-day observations on several cases of premenstrual syndrome showed varying degrees of weight gain, oedema, hypertension, and albuminuria occurring during the premenstruum, as is illustrated by the following cases.

Case 3.—Childless housewife aged 40, suffering from premenstrual headaches, depression, and irritability. Albuminuria had been detected on many isolated occasions in the previous 11 years, but on investigation had been diagnosed as orthostatic albuminuria. Observations over two cycles showed the blood pressure to rise from 110/70 mm. Hg after menstruation to 140–160/80 mm. Hg in the premenstruum, and the albuminuria (in catheter specimens) was limited to the five premenstrual days. Treatment with 10 mg. of progesterone brought relief from all symptoms, blood pressure remained steady at 110/70 mm. Hg, and no albuminuria was detected during the menstrual cycles.

Case 4.—Childless housewife aged 42, suffering from premenstrual headache, depression, oedema, and dyspnoea. Observation revealed a weight gain of 11 lb. (5 kg.)—from 7 st. (44.5 kg.) after menstruation to 7 st. 11 lb. (49.5 kg.)—during the premenstruum—ankle circumference increased from 7¾ in. (19.7 cm.) to 9⅝ in. (24.5 cm.), and albumin (3/1,000 Esbach) was present in the premenstruum. Moist sounds were heard in the bases of both lungs at the height of the oedema. Blood pressure was 200–250/120–130 mm. Hg throughout the cycle. When treated with 50 mg. of progesterone on alternate days she became symptom-free, her weight remained steady at 7 st. (44.5 kg.), ankle circumference fell to 7¼ in. (18.4 cm.), no albuminuria was detected, and no abnormal sounds were heard in the lungs. Blood pressure remained at 190–230/120–130 mm. Hg.

Case 5.—Club hostess, widow, aged 40, unemployed for six months owing to premenstrual epilepsy and bilious headaches. Her only pregnancy had been terminated at 28 weeks by caesarean section for chronic nephritis. The blood pressure rose from 120–130/80–110 mm. Hg during the postmenstruum to 190/110 mm. Hg immediately before a premenstrual epileptic fit, the weight rose from 9 st. 2 lb. (58 kg.) to 9 st. 6 lb. (60 kg.), and ankle circumference from 7½ in. (19 cm.) to 8½ in. (21.6 cm.). Albumin (3–5/1,000 Esbach) was present throughout the cycle. When treated with 25 mg. of progesterone daily she became symptom-free, the blood pressure remained at 110/80 mm. Hg, weight steady at 9 st. 2 lb. (58 kg.), but albuminuria persisted at the same level.

These three cases can be recognized as analogous to the three classes found in toxaemia of pregnancy—namely, the commonest where, after a normal early pregnancy, there is a later development of toxaemic signs; those with hypertension in early pregnancy who later develop oedema and albuminuria; and those with albuminuria in early pregnancy who later develop hypertension and oedema. These cases also demonstrate the specificity of progesterone in acting only on those symptoms and abnormal signs present in the premenstruum, but not on abnormal signs present throughout the cycle. No previous studies have been traced of the occurrence of oedema, hypertension, or albuminuria limited to the premenstruum, nor of the specific action of progesterone in relieving these premenstrual signs.

Early Signs of Toxaemia

Cummings (1934) was the first to point out that the earliest sign of impending toxaemia is excessive weight gain in the middle trimester. Morton (1950), on the other hand, reported a definite weight gain in 52% of women suffering from premenstrual syndrome. Thomas (1933) reported two cases of massive oedema with weight gains of 8–12 lb. (3.6–5.4 kg.) coinciding with menstruation, and noted the subsequent diuresis accompanying the return to normal weight. Interest in these two cases is increased by the observation that one woman dated the onset of her condition to an eclamptic pregnancy and the other showed albuminuria at the height of the oedema. That the weight gain in both premenstrual syndrome and toxaemia of pregnancy is due to water retention is shown by the oliguria which accompanies the symptoms, and the spontaneous diuresis which occurs at the end (menstruation or labour), coinciding with a return to normal weight. Theobald (1950) has reported that in toxaemia the urinary output may exceed fluid intake by more than 6 litres in the second to fifth days of the puerperium, while Case 4 had gained 12 lb. (5.4 kg.) in the premenstruum, which she lost in two days by the diuresis she had always noticed to coincide with the onset of menstruation. It is well known that a copious flow of pale clear urine may mark the end of an acute attack of migraine or asthma.

Epilepsy in Relation to Eclampsia

There is no recognized relationship between an epileptic and eclamptic fit, although the character of the fit is identical; but Walshe (1952) noted that women show a special proneness to epileptic fits the day before menstruation; Dexter and Weiss (1941) have given a detailed account of the "unusual sequel" of idiopathic grand mal occurring after eclampsia; and Frohlich (1953) reported five cases of premenstrual epilepsy, in one of which the onset of epilepsy followed eclampsia. In the present investigation it was found that one eclamptic mother subsequently developed epilepsy, and of six pre-eclamptic mothers one subsequently developed grand mal and five had petit mal. In the following case epilepsy followed eclampsia and responded to ethisterone after 27 years' duration.

Case 6.—A housewife aged 63, gravida-5, had had her first and fourth pregnancies complicated by placenta praevia. Her fifth pregnancy occurred at the age of 36. She received no antenatal care, and at 37 weeks had seven eclamptic fits followed by the spontaneous delivery of a stillborn child. She recalled that this pregnancy had differed from previous ones in that she had felt ill throughout, and had suffered from severe headaches, preceded by an aura of black spots before her eyes. She is definite there was no oedema of ankles. She had since suffered from epilepsy and permanent right foot-drop. Fits occurred several times a week every three to four weeks and were worse at her periods. She had a normal menopause at 52 years, and since then several fits had occurred every two weeks. The fits resulted in complete loss of consciousness, were preceded by the same visual aura as noticed during her pregnancy, and were followed by severe headache lasting all day. When first seen in September, 1953, she was averaging six fits a fortnight in spite of phenobarbitone, 1 gr. (65 mg.) three times a day, and sodium phenytoin, 1.5 gr. (0.1 g.) three times a day. She had no albumin or oedema, and blood pressure varied between 160–140/110–90 mm. Hg. She was treated with ethisterone, 25 mg. three times a day, without any sedatives, and has reported no fits in the subsequent eight months.

This study has disclosed three stages in the development of both premenstrual syndrome and toxaemia of pregnancy. The earliest is the stage of minor symptoms, in which each individual's symptoms are of the same nature in the premenstruum and in pregnancy. As the disease advances, the stage of signs occurs with weight gain, oedema, hypertension, and albuminuria, and finally both diseases culminate in the stage of fits, either epileptic or eclamptic.

Treatment

In my practice 29 toxaemic mothers received treatment for premenstrual syndrome. Relief was obtained from progesterone injections in 18 cases and from ethisterone in the remaining 11. Six cases subsequently received a progesterone implant to provide prolonged action. These premenstrual symptoms, which were relieved by progesterone, were the same as occurred during toxaemia of pregnancy. In view of this common symptomatology a trial of progesterone therapy for toxaemia of pregnancy was undertaken.

Progesterone therapy in toxaemia was based on knowledge gained from its use in premenstrual syndrome. Experience has shown that for successful use progesterone must be administered before premenstrual symptoms begin, usually from the 14th to the 28th day, or throughout the cycle. Progesterone first administered during an acute attack of migraine, asthma, epilepsy, or depression will not lessen the symptoms or shorten the duration of attack, although, occasionally, rapid relief of premenstrual symptoms during an acute attack will follow the combined injection of progesterone, 25–50 mg., and mersalyl, 2 ml. It was found necessary to give progesterone in oil daily or on alternate days; larger doses did produce a longer duration of effect. Signs of overdosage of progesterone were euphoria, insomnia, restless energy, and dysmenorrhoea (which in pregnancy may resemble false labour). Severe overdosage may result in temporary faintness, sudden lowering of blood pressure, and muscular weakness of a myasthenic type. Progesterone may delay the onset of menstruation, and there is some evidence that it may also delay the onset of labour (Robson and Paterson, 1937). Deep intramuscular injections into the buttocks and avoidance of contamination of the outside of the needle with progesterone are necessary precautions to avoid urticarial weals from the presence of progesterone in the dermis. Ethisterone has the advantage of oral administration, but its dosage was found to be very variable. In some cases twice as much ethisterone was necessary to equal the effect of progesterone, sometimes a tenfold dose was required, but in others doses of

500 mg. of ethisterone daily were ineffective in bringing the relief which occurred with daily injections of 10 mg. of progesterone.

The scheme of progesterone therapy was formulated upon the recognition of the stage of minor symptoms preceding the development of toxaemic signs, and the belief that the severity of minor symptoms is related to the degree of progesterone deficiency. At routine antenatal visits patients were asked about the presence of nausea, headache, vertigo, and lethargy. If these or any other minor symptoms were reported an immediate injection of progesterone, 25–50 mg., was given, and the patient was seen again in three days. If symptomatic relief followed the test injection, that symptom was regarded as that patient's earliest indication of toxaemia, but if no relief followed some other cause for the symptom was sought. Minor symptoms were then treated with ethisterone, 10–250 mg. daily, or progesterone, 10–150 mg. daily or on alternate days, the dosage being raised until the patient was completely symptom-free, the interval between injections being gauged by the duration of relief following the test injection. Treatment was continued on a symptomatic basis, continuing while symptoms persisted and with an increase of dose if symptoms recurred. All patients were ambulant throughout and no dietary instructions were given.

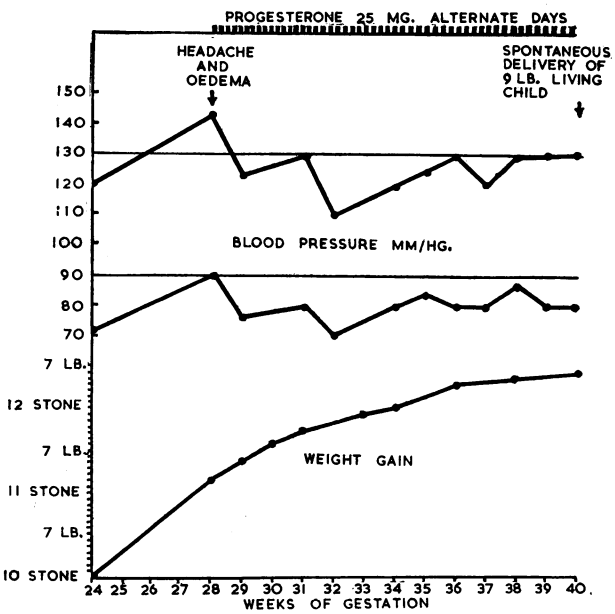

FIG. 3.—Case 7. Mild toxaemia treated with progesterone.

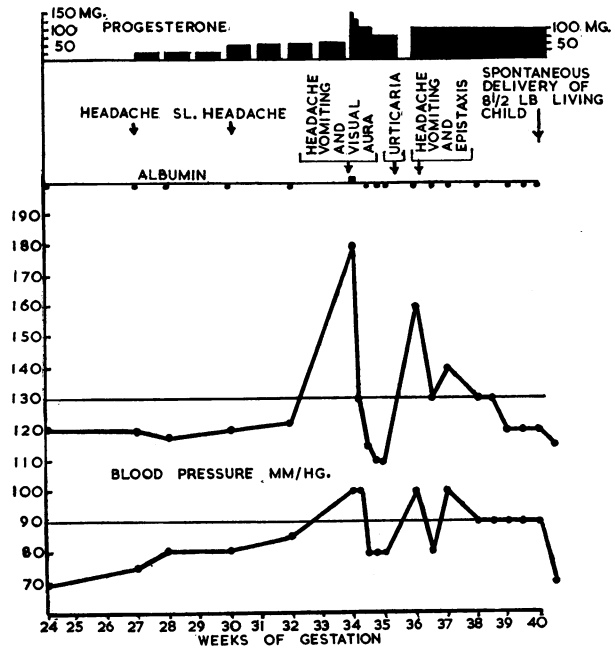

FIG. 4.—Case 8. Severe toxaemia treated with progesterone. The black dots below the albumin line indicate that no albumin was present.

Vomiting of early pregnancy was regarded as an early sign of toxaemia, for, while most cases cease spontaneously after the fourth month, it is recognized that many who continue vomiting throughout their pregnancy later develop toxaemia. Progesterone brought speedy and complete relief to 34 cases (100%) of vomiting of early pregnancy. Ten cases of moderate and one case of severe toxaemia have been treated on these principles, and all have gone successfully to full term without bed rest or surgical intervention and with the delivery of live babies. Cases 7 and 8 illustrate the use of progesterone in one case of moderate and one case of severe toxaemia (Figs. 3 and 4).

Case 7.—A housewife, aged 25 years, gravida-3, had had progesterone treatment for premenstrual syndrome with left hemicranial headache and lassitude, which followed her second pregnancy in 1950. In 1952 she became pregnant, with blood pressure 105–120/70 mm. Hg in the early months. At 28 weeks she complained of hemicranial headaches and bloatedness, had gained 16 lb. (7.3 kg.) in the previous four weeks, had oedema limited to the ankles, no albuminuria, and blood pressure of 145/90 mm. Hg. Progesterone, 25 mg., was given on alternate days. At 29 weeks she was symptom-free, had gained 3 lb. (1,360 g.) in one week, had slight oedema of ankles, and her blood pressure had fallen to 126/76 mm. Hg. The same dose of progesterone was continued throughout as she remained symptom-free. She had a spontaneous delivery at full term of a living child. (Fig. 3.) An extract of the pathologist's report of placenta read: "Cut surface shows spongy dark-red tissue throughout, with occasional small yellowish deposits of fibrin. Histology; normal placenta."

Case 8.—A housewife aged 35, gravida-2, developed toxaemia at 36 weeks during her first pregnancy and was admitted to hospital with a blood pressure of 180/110 mm. Hg. No improvement in hypertension or albuminuria with rest; surgical induction at 38 weeks. Uterine inertia in first stage and then a high forceps delivery of a living child. Duration of labour, 3 days 12 hours. Her second pregnancy, in 1953, began with blood pressure 120/70 mm. Hg. At 27 weeks she complained of lassitude, spots before her eyes, and nausea; no abnormal signs; obtained symptomatic relief for 24 hours following test dose of progesterone, 25 mg. She was given progesterone, 25 mg. daily, until the 30th week, when the dose was increased to 50 mg. daily for recurrence of headache. At 34 weeks she had a recurrence of severe headache with visual aura and vomiting. It was on a Monday, and the patient explained that symptoms were always worse on Mondays; for the nurse who gave daily injections did not come on Saturday or Sunday. She had oedema of ankles and face, a trace of albumin, and a blood pressure of 180/102 mm. Hg. She was given an immediate injection of progesterone, 150 mg., and mersalyl, 2 ml. The following day she felt better, and although the oedema was more marked her blood pressure had dropped to 130/100 and no albumin was present. Progesterone, 125 mg., was given. Two days later the oedema had disappeared, her blood pressure was 118/80, and she was completely symptom-free. She remained on a daily dose of progesterone, 75 mg., until the 36th week, when she developed an urticarial rash at the injection site. As she was completely symptom-free, injections were stopped for two days, but there was a recurrence of headache, vomiting, and epistaxis on the second injection-free day, and the patient was most anxious to return to injections. Her blood pressure had risen to 160/100, but there was no oedema or albuminuria. Progesterone, 100 mg., was then given daily until full term, when after a six-hour normal labour she produced a living 8¼-lb. (3.9-kg.) child. (Fig. 4.) The pathologist reported: "The maternal aspect is firm and brown, and cut surface shows spongy reddish tissue with a few yellowish areas suggesting fibrin deposition, not infarction. Histology: solitary infarct in one, and considerable fibrin deposition in fibrosing senile placenta."

This dramatic fall in blood pressure in Case 8 and improvement in general well-being in an ambulatory patient with severe toxaemia is of the type one associates with specific therapy.

Robson and Paterson (1937) demonstrated that convulsions, acute toxic conditions, and later death could be produced experimentally in rabbits during the latter half of pregnancy when they were deprived of the secretion of the luteal hormone or of gonadotropic hormone. They suggested that toxaemia in human pregnancy might also be associated with insufficiency of luteal secretion, and tested their hypothesis by treating 12 women suffering from severe toxaemia with daily doses of progesterone, 5 mg. for three to four days, and thereafter at longer intervals. They describe their results as encouraging. Clinical trials of progesterone were then undertaken by Marsden (1937), Young (1937), Paterson (1938–9), McMann (1938), and by Bennett, who in 1939, after reviewing all trials, concluded: "It is unlikely that progesterone treatment will ever find a permanent place in routine treatment of toxaemia."

In treatment of premenstrual syndrome it was found that the daily dose of 10–50 mg. of progesterone was necessary for symptomatic relief. The smallness of progesterone dosage in early trials might explain Bennett's conclusions, especially in view of Hoffmann and v. Làm's (1948) finding that in normal pregnant women at full term the progesterone level is raised some fifty times the normal non-pregnant value for the premenstruum. This suggests that, for complete progesterone substitution therapy, doses of 500 mg. or possibly even 2,500 mg. daily may be required. Dosages as high as 300–500 mg. daily have been used in non-pregnant women without side-effects in clinical trials on the value of various steroids in the treatment of rheumatoid arthritis (Copeman *et al.*, 1950). Thus Bennett's conclusion may be likened to the condemnation of insulin through its failure to relieve diabetic coma when used in a dose of less than one unit daily. It is also possible that progesterone substitution therapy should be started in the early stages of its deficiency and before the development of toxaemic signs.

The finding of low urinary oestrogen and pregnanediol output in toxaemic mothers by Smith and Smith (1938) led White (1947) to apply hormone substitution therapy to diabetic mothers, who are particularly prone to develop toxaemia of pregnancy. She gave stilboestrol and progesterone in daily doses of 5 mg. of each at 20 weeks, increasing to 30 mg. daily of each at term, and was able to claim a greatly lowered incidence of toxaemia. Oakley (1953), using similar hormone substitution therapy of the same dosage, but giving ethisterone instead of progesterone, was unable to report similar success. It has already been mentioned that ethisterone treatment of the premenstrual syndrome showed considerable individual variation in dosage requirements and results obtained in comparison with progesterone. Martindale (1952) states that the oral dose of ethisterone is approximately six times the injection dose of progesterone; therefore the substitution of ethisterone for progesterone at the same dosage cannot be expected to provide comparable results, and may explain Oakley's failure to repeat White's success.

Personal experience has shown that oestrogen administration increases the severity of premenstrual syndrome, thus confirming the findings of Israel (1938), and is to be expected if excessive oestrogen (Frank, 1931; Morton, 1950) or a high oestrogen–progesterone ratio (Israel, 1938; Greene and Dalton, 1953) is the cause of this syndrome. Oestrogens have been shown to produce oedema, clinically by Mazer and Israel (1951) and experimentally by Zuckerman and his colleagues (Krohn and Zuckerman, 1936; Aykroyd and Zuckerman, 1938; Zuckerman *et al.*, 1938) and by Gillman (1942). The similarity of the nausea of early pregnancy to the nausea induced by oestrogen administration was first noticed by Hirst (1918), and was confirmed by Finch (1942) and Patton (1949). Experimental work on rabbits has shown that the progestational effect of one unit of progesterone may be inhibited by 1/75th that amount of oestrone (Robson, 1947). Thus the use of stilboestrol combined with progesterone at equal dosage, as suggested by White in the prophylaxis of toxaemia, may be sufficient to inhibit the action of progesterone in the treatment of toxaemia.

Conclusion

From the foregoing the impression might be formed that toxaemia is an inevitable sequel to premenstrual syndrome, but Greene and Dalton (1953) reported that the incidence of toxaemia in their series was 19% and noted also that 62% of the women actually felt better than usual after the first trimester of pregnancy. During pregnancy the placenta provides an additional source of progesterone, which is produced in significant quantities after the end of the first trimester. Thus it is possible that in sufferers of premenstrual syndrome, if the placental production of progesterone is sufficient, no toxaemia will result, while if there is an excess of placental progesterone there will be a natural amelioration of recurrent symptoms. It was observed that many sufferers from premenstrual syndrome, who were symptom-free during pregnancy, made the significant remark when receiving progesterone: "I feel wonderful—just as if I were pregnant." On the other hand, should placental progesterone be insufficient at the time when the corpus luteum ceases to supply progesterone, a toxaemic pregnancy will result, unless the supply is made up from an extraneous source.

The corpus luteum is under the control of the gonadotropic hormone from the pituitary. Thus the progesterone deficiency of premenstrual syndrome may result from insufficient corpus luteal secretion or insufficient gonadotropic hormone; and the deficiency in toxaemia may result from insufficient gonadotropic hormone or insufficient placental progesterone. May it not be that a sufferer from premenstrual syndrome with progesterone deficiency resulting from corpus luteum may yet have sufficient gonadotropic hormone to stimulate, or even excessively stimulate, the placental production of progesterone? This would result in the natural alleviation of recurrent symptoms and the feeling of well-being during pregnancy as reported by Greene and Dalton in 62% of women suffering from premenstrual syndrome. Alternatively, where the progesterone deficiency is due to insufficient gonadotropic hormone, sufferers from premenstrual syndrome may also have insufficient stimulation from gonadotropic hormone to produce adequate placental progesterone, resulting in the development of toxaemia.

Summary

An investigation into the incidence of premenstrual syndrome in 952 women showed the high incidence of 86% among those who had suffered from toxaemia of pregnancy, compared with 26% in controls.

A stage of minor symptoms preceding the onset of toxaemic signs is reported, and these same symptoms tend to occur in the premenstruum.

Observations on women suffering from premenstrual syndrome showed presence of oedema, hypertension, and albuminuria in the premenstruum and the spontaneous disappearance of these symptoms with menstruation.

Both premenstrual syndrome and toxaemia of pregnancy appear to have three stages of development—a stage of symptoms, followed by signs (oedema, hypertension, and albuminuria), and culminating in fits, either epileptic or eclamptic.

Following the successful use of progesterone in premenstrual syndrome, a scheme of treatment for toxaemia is suggested, based on the recognition of the early symptomatic stage. The successful treatment with progesterone of 10 cases of moderate severity and one case of severe toxaemia are reported.

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REPORT ON THE USE OF GAMMA GLOBULIN AND ADULT SERUM FOR MEASLES PROPHYLAXIS IN ENGLAND AND WALES, 1949-53

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Gamma globulin prepared by the method of Kekwick and Mackay (1954) was shown in a Report to the Medical Research Council (Report, 1950) on a series of controlled trials in day nurseries to be superior to adult serum for measles prophylaxis. Since 1949 gamma globulin produced on behalf of the Medical Research Council and Ministry of Health at the Lister Institute has been distributed, mainly for measles prophylaxis, by the Public Health Laboratory Service. It is issued in ampoules containing 250 mg. of protein, 96% of which is gamma globulin. The contents of each ampoule are derived from the fractionation of approximately 40 ml. human serum or about 48 ml. human plasma, and are dissolved in 3 ml. of sterile distilled water before injection.

During the same period irradiated adult serum—that is, serum from normal adults which has been exposed to ultra-violet light—has also been distributed for measles prophylaxis. Until February, 1951, the adult serum was issued at normal strength in 5-ml. or 10-ml. doses; thereafter it was concentrated to one-third its original volume, so that a 5-ml. ampoule contained the equivalent of 15 ml. of normal serum.

All doctors using the three prophylactics—gamma globulin, unconcentrated adult serum, and concentrated adult serum—were asked to complete a standard form reporting the results they obtained. During the period October 1, 1949, to December 31, 1953, report forms were returned for 82% of the 12,408 doses of globulin and 67% of the 3,931 doses of adult serum issued. These forms were analysed with three aims in view: (1) to obtain information on how measles prophylactics were used, so that the demand might be more satisfactorily met in future; (2) to determine the incidence of local and general reactions to inoculation; and (3) to gain some indication of the influence of dosage, the age of the person injected, and the period between exposure and inoculation on the prophylactic effect.

In the analysis all forms returned were used in the study of the distribution of measles prophylactics and of reactions to inoculation, but only those relating to 4,080 home contacts under 5 years of age were used to study the prophylactic effect. Full details of dosage and result were available for 3,846 of these, 2,760 of whom had received gamma globulin, 375 unconcentrated adult serum, and 711 concentrated adult serum.

Home contacts were selected because they were almost certainly exposed to infection, and if untreated most of them would have been attacked. The incidence of measles among susceptible children of different ages exposed to infection in another member of the same family has, in past studies, been remarkably constant. Family secondary attack rates noted by various observers are set out in Table I for children at different ages under 5 years and averages calculated from them. In the absence of any untreated but otherwise similar control group these average rates give the best available estimate of what might have been expected if no prophylactic had been used. On this basis about 9% of susceptible children under 6 months of age, about 70% over 6 months and under 1 year, about 88% over 1 year and under 3 years, and about 89% over 3 and under 5 years would have been expected to develop measles when exposed to another case in the same family.

As gamma globulin and adult serum were not allocated to contacts at random it is possible that those who received gamma globulin differed in some relevant respect from those who received adult serum. This should be borne in mind when the results with gamma globulin and adult serum are compared. It is also possible that if all the forms had been returned instead of 80% different results might have been obtained.

Distribution of Measles Prophylactics

In relation to population and to incidence of measles, London and the South-east of England received much more gamma globulin than other parts of the country. In London and the South-east about 10 contacts were inoculated for every 1,000 cases notified, compared with about 3 contacts for every 1,000 cases in other regions. Steps have now been taken to ensure a more uniform distribution throughout the country. Three-fifths of the gamma globulin was used in hospitals and two-fifths in general practice. These proportions were roughly reversed for adult serum. Of the gamma globulin used in general practice 77% was administered to children less than 3 years of age, so it is already being used in the main for young children, and little further